Remarks

Interview Summary

Applicants appreciate the courteous reception by examiners Nancy Vogel and Catherine Hibbert on July 16, 2009, to inventor Victor Velculescu and the undersigned. The inventor presented an explanation of the claimed method and the experiments using the claimed method. The experiments and data discussed were those provided in the specification as originally filed. The examiners pointed to particular claim language which they construed as not adequately defining and distinguishing the invention from the prior art.

Amendments

The claims have been amended for clarification purposes. It is respectfully submitted that them amendments do not add new matter. Amendments to the claims are shown below with specification support indicated. Minor amendments constituting insignificant changes from their predecessors are not listed.[1]

Claims	Recitation	Specification Support and Location
90, 99	sequencing a population of pieces of the genome of the test eukaryotic cell to provide nucleotide sequence of said	"Populations of sequence tags…" [19]

1 Applicants would be happy to point out support for any amendment not already listed in the table.

	pieces;	"determining the identity of the sequence tags…Preferably the determination of identity of the tags is done by automated nucleotide sequence determination." [21]
90, 99	matching, *in silico,* pieces of the genome to genomic locations using the nucleotide sequence of said pieces;	"Tags were computationally extracted from sequence data, matched to precise chromosomal locations…. " [25] "Tags were ordered along each chromosome…." [27] "The experimentally derived genomic tags obtained from NLB, DiFi and Hx48 cells were electronically matched to these virtual tags." [35]
90	counting the pieces within windows of a selected size throughout the genome to determine number of pieces as a function of genomic location, wherein each window comprises a plurality of genomically clustered pieces;	"recording the number of occurrences of each such tag or of genomically clustered tags." [21] "The plurality of sequence tags are within a window of sequence tags which are calculated to be contiguous in the genome of the species of the eukaryotic cell." [06]

		"Moving windows containing the same number of virtual tags as the simulated alteration were used to evaluate tag densities along the genome." [34]
90	comparing the number of pieces enumerated within each window for the test eukaryotic cell to the average number of pieces in windows of the selected size throughout the genome to obtain piece densities per window, wherein the piece densities per window represent the karyotype of the genome of the test eukaryotic cell.	"Tag densities for sliding windows containing N virtual tags were determined as the sum of experimental tags divided by the average number of experimental tags in similar sized windows throughout the genome." [35] "Changes in copy number of portions of the genome can be determined on a genomic scale." [15]
99	dynamically counting the pieces within a moving window of a selected size to determine number of pieces as a function of genomic location, wherein the window comprises a plurality of genomically clustered pieces;	"Finally, tags are computationally extracted from sequence data, matched to precise chromosomal locations, and tag densities are evaluated over moving windows to detect abnormalities in DNA sequence content (Step 7)." [25]

		"Tag densities were dynamically analyzed in windows ranging from 50 to 1000 virtual tags." [35] "Digital Karyotype values represent exponentially smoothed ratios of DiFi tag densities, using a sliding window of 1000 virtual tags normalized to the NLB genome." [11] "Tag densities were analyzed along each chromosome using sliding windows containing 1000 virtual tags (~4 Mb) as windows of this size were predicted to reliably detect such alterations (Table 1)." [28]
99	comparing the number of pieces enumerated within the window at a genomic location to an average number of pieces in windows of the selected size throughout the genome to obtain piece density per window, wherein a	"Tags were ordered along each chromosome, and average chromosomal tag densities, defined as the number of detected tags divided by the number of virtual tags present in a given chromosome, were evaluated (Table 2)." [27]

	difference in piece density per window between windows reflects a difference in copy number between portions of the genome.	"Tag densities for sliding windows containing N virtual tags were determined as the sum of experimental tags divided by the average number of experimental tags in similar sized windows throughout the genome." [35] "For the NLB sample, tag density maps showed uniform content along each chromosome, with small variations (<1.5 fold) present over localized regions, presumably due to overrepresentation of tags matching repeated sequences (data not shown). In contrast, the DiFi tag density map (normalized to the NLB data) revealed widespread changes, including apparent losses in large regions of 5q, 8p and 10q, and gains of 2p, 7q, 9p, 12q, 13q, and 19q (Fig. 2 and Fig. 5)." [28]
111	The method of claim 90 or 99 wherein the sequencing is performed by automated nucleotide sequence	"Preferably the determination of identity of the tags is done by automated nucleotide sequence determination." [21]

	determination.	
112	The method of claim 90 or 99 wherein between 100,000 and 1,000,000 pieces are sequenced and matched.	"PPVs [positive predictive values] were calculated from 100 simulated genomes, using 100,000 or 1,000,000 filtered tags, and shown in the table as percents." Table 1 and its legend. "We characterized 210,245 genomic tags from lymphoblastoid cells of a normal individual (NLB) and 171,795 genomic tags from the colorectal cancer cell line (DiFi) using the mapping and fragmenting enzymes described above." [27]
113	comparing piece densities per window for the test eukaryotic cell to piece densities of a reference eukaryotic cell.	"Estimates of chromosome number using observed tag densities normalized to densities from lymphoblastoid cells suggested a highly aneuploid genetic content, with $\leq$1.5 copies of chromosome 1, 4, 5, 8, 17, 21 and 22, and $\geq$3 copies of chromosome 7, 13 and 20 per diploid genome." [27]

114	The method of claim 90 or 99 wherein the selected size is less than or equal to 40 kb.	"Thus, for example, a window can comprise sequence tags that map within about 40 kb, about 200 kb, about 600 kb, or about 4 Mb." [22]
115	The method of claim 90 or 99 wherein the selected size is less than or equal to 200 kb.	"Thus, for example, a window can comprise sequence tags that map within about 40 kb, about 200 kb, about 600 kb, or about 4 Mb." [22] "…a window size of 50 virtual tags (~200 kb) was used…" [29]
116	The method of claim 90 or 99 wherein the selected size is less than or equal to 600 kb.	"Thus, for example, a window can comprise sequence tags that map within about 40 kb, about 200 kb, about 600 kb, or about 4 Mb." [22] "Using a window size of 150 virtual tags (600 kb)…." [31]
117	The method of claim 90 or 99 wherein the selected size is less than or equal to 4	"Thus, for example, a window can comprise sequence tags that map within about 40 kb,

	Mb.	about 200 kb, about 600 kb, or about 4 Mb." [22] "…using sliding windows containing 1000 virtual tags (~4 Mb)…." [28]

It is respectfully submitted that no new matter is added by this amendment.

The Rejection of Claims 90, 92-95, 97-107, and 109-110 Under 35 U.S.C. § 102(a)

Claims 90, 92-95, 97-107, and 109-110 stand rejected as anticipated by Bensimon.[2] This rejection is respectfully traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the ... claim. *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis* verbis test, *i.e.,* identity of terminology is not required. *In re Bond,* 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

Bensimon's teachings are substantially different from the subject invention. While applicants do not concede that the claims as previously presented read on the Bensimon teaching, the claims have been amended to clarify the distinctions between the invention and the prior art. Bensimon does not fall within the scope of the claims as amended.

[2] US Patent Application 2002/0048767.

Bensimon does not teach any of the four steps of either of the only independent claims, claims 90 and 99. Claim 90 requires sequencing, matching *in silico,* counting pieces with windows, and comparing number of pieces within windows. Claim 99 requires sequencing, matching *in silico,* dynamically counting pieces within a moving window, and comparing number of pieces within a window at a genomic location to an average number of pieces.

Bensimon does not teach sequencing of pieces of the genome to provide nucleotide sequence of the pieces. Bensimon was cited as identifying pieces of the genome by hybridization to a known probe. Bensimon does not teach identification by sequencing.

Bensimon identifies pieces of the genome by means of the previously mentioned hybridization to known probes. Bensimon does not computationally (*in silico)* match pieces to genomic locations using a nucleotide sequence determined by sequencing of pieces.

Bensimon does not count pieces with a moving window of a selected size or within windows of the selected size, wherein the window(s) comprises a plurality of genomically clustered pieces. Bensimon does not teach this method or concept which permits sampling rather than saturation of the genome.

Bensimon does not compare the number of pieces that are counted within windows to an average number of pieces in windows of the same (selected) size.

Bensimon teaches none of the four steps of the methods of the independent claims. Bensimon therefore does not teach "each and every element as set forth in the claim." Bensimon does not qualify as an anticipating reference of the independent claims or any of the dependent claims, which by definition require at least the elements of the independent claims.

Withdrawal of the rejection is respectfully requested.

The Rejection of Claims 96 and 108 under 35 U.S.C. § 103(a)

Claims 96 and 108 stand rejected as obvious over Bensimon (*supra*) in view of Kong (US 5200336). This rejection is respectfully traversed.

In order to make a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The U.S. Patent and Trademark Office must make a finding that the prior art included each element claimed, although not

necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference. M.P.E.P., 8th ed., § 2143.

Claims 96 and 108 are dependent from claims 90 and 99, respectively. For at least the reasons detailed above, Bensimon does not teach the methods of claims 96 and 108. Kong's teaching of BcgI and its recognition and cleavage patterns does not cure the inadequacies of Bensimon in teaching the methods of claims 90 and 99. None of the steps of the independent claims are not taught by ***either*** Bensimon or Kong. Thus even combining the two teachings, the elements of claims 96 and 108 is not taught.

Because so much of the present invention is not taught or in any way suggested by the cited references, the rejection fails to present a *prima facie* case of obviousness. Withdrawal is therefore respectfully requested.

Conclusion

Applicants respectfully request that the patentability of the current set of claims be reconsidered. Applicants request that the next communication from the Patent Office be a Notice of Allowance.

Respectfully submitted,

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